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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,721	MCCART ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15,17,18,25 and 45-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15,17,18,25 and 45-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is reply to the Paper filed 14 November 2005 in response to the Non-Final Office Action mailed 12 May 2005. Claims 1-13, 15, 17, 18, 25 and 27 were considered in the 12 May Office Action. Claim 27 was canceled, claims 1-13, 15, 17, 18 and 25 were amended and claims 45-50 were added in the 14 November Paper. Claims 1-13, 15, 17, 18, 25 and 45-50 are pending and under consideration.

Response to Amendment

Rejection of claim 27 is rendered moot by the cancellation thereof.

Claim Rejections - 35 USC § 103

Claims 1-12, 15, 17 and 25 stand rejected and newly added claims 45-48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* (1995) WO 95/31105 in view of Dorner *et al.* U.S. Patent No. 6,103,244 and in view of Buller *et al.* (1988) *J. Virol.* 62:866-874 (previously made of record) for the reasons set forth in the 12 May Office Action at pages 4-8 and herein below under "*Response to Arguments*".

It was concluded based on an analysis of claims and art according to the factual inquiries set fort in *Graham* v. *John Deere Co.* that the tumor cell of claims 1-12, 15, 17, 25, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. In view of the fact that the tumor cell of Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* would comprise a recombinant WR strain vaccinia virus having each of the limitations of the vaccinia virus comprised within the composition of matter of the amended

claims 1-12, 15, 17 and 25, the composition of matter would also be obvious over the tumor cell of the cited art.

Furthermore, the limitations of newly added claims 45-50 would also have been obvious over Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* Buller *et al.* teaches that the vaccinia virus vector comprising a disruption of the VGF gene comprises a beta-galactosidase gene inserted into the VGF (see especially Figure 1 and the caption thereto), which beta-galactosidase insertion meets the limitations of claims 45 and 47; Dorner *et al.* teaches insertion of a polylinker into the TK gene to facilitate the subsequent insertion of heterologous genes that would inactivate said TK gene according to the limitations of claim 46 (see especially Figure 4.2 and the caption thereto, and column 30, full paragraph 3); and Mastrangelo *et al.* teaches that the vector should comprise an exogenous nucleic acid sequence, wherein the exogenous nucleotide sequence is a cytokine encoding gene according to claim 48 (see especially the first full paragraph on page 6).

Claim 50 recites that the exogenous nucleotide sequence is an imaging agent. As the specification does not contain an explicit definition of the metes and bounds of an "imaging agent" the limitation is broadly construed as encompassing any nucleotide sequence that can be specifically detected and imaged by, for example, nucleic acid hybridization or by immunological detection of a polypeptide encoded thereby. As essentially all nucleic acids meet this definition, including the nucleic acids comprised in the vectors of the cited art, the limitations of claim 50 are also obvious over the cited art.

Claims 1 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* as applied to claim 1 above, and further in view of Zhang *et al.* (1996) *Biochem. Biophys. Res. Commun.* 227:707-711 for the reasons set forth at pages 8-9 of the 12 May Office Action and herein below under "*Response to Arguments*".

As stated in the 12 May Office Action, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the EGFP marker gene of Zhang *et al.* for the *LacZ* gene of Buller *et al.* according to the limitations of the instant claim 18 and the invention of claims 1 and 18, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. In view of the fact that the tumor cell of the cited art would comprise a recombinant WR strain vaccinia virus having each of the limitations of the vaccinia virus comprised within the composition of matter of the amended claims 1 and 18, the composition of matter would also be obvious over the tumor cell of the cited art.

Claims 1, 12 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* as applied to claims 1 and 12 above and further in view of Paoletti U.S. Patent No. 5,942,235 for the reasons set forth at pages 9-10 of the 12 May Office Action and herein below under "*Response to Arguments*".

As stated in the 12 May Office Action, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* to include the tumor specific antigen p53 according to the teachings of Paoletti and the invention of claims 1, 12 and 13, as a whole, would

have been obvious to one of ordinary skill in the art at the time the invention was made. In view of the fact that the tumor cell of the cited art would comprise a recombinant WR strain vaccinia virus having each of the limitations of the vaccinia virus comprised within the composition of matter of the amended claims 1 and 18, the composition of matter would also be obvious over the tumor cell of the cited art.

Response to Arguments

In the discussion commencing in the second full paragraph on page 7 of the 14 November Paper, Applicant urges that the instant claims are not obvious over the cited art in view of the experimental section of the instant specification and the post-filing disclosure of McCart *et al.* (2001) *Cancer Res.* 61:8751. Applicant cites experiments wherein it was found that resting cells infected with TK and VGF double-deleted vaccinia virus produced less virus than resting cells infected with wild-type, TK-, or VGF- vaccinia virus while tumor cells infected with TK and VGF double-deleted vaccinia virus produced an equivalent amount of virus relative to cultures infected with wild-type, TK-, or VGF- vaccinia virus. Applicant argues that these findings of tumor selectivity are unexpected and, therefore, the claimed invention, as a whole, would not have been obvious at the time the invention was made.

These arguments have been fully considered but are not deemed persuasive. First, the submission is not a proper showing of unexpected results. MPEP 716.01 II. states, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include

statements regarding unexpected results..." MPEP 716.02(g) states, "'The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001.' Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. Ex parte Gray, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989)." Thus, the submission of a published document and attorney arguments cannot be accepted as evidence of unexpected results.

Furthermore, even if the McCart *et al.* publication had been submitted in the form of an affidavit or declaration, the evidence would not establish that the properties of the TK and VGF double-deleted vaccinia virus are unexpected. First, Buller *et al.*, one of the references used in the rejection, teaches that deletion of the VVGF gene results in reduced virus production from resting cells relative to wild-type virus, while the production of VVGF gene deleted virus from actively dividing cells was not different from wild-type virus (see especially Figure 5A and the caption thereto, and the paragraph bridging the left and right columns on page 870). In the second full paragraph in the right column on page 8751, McCart *et al.* teaches "A TK- virus requires TTP for DNA synthesis from the nucleotide pool present in dividing cells. This leads to preferential viral replication in dividing cells and is the presumed explanation for the observed tumor specificity", and in the paragraph immediately following that statement McCart *et al.* teaches, "VGF is a secreted protein produced early in viral infection and acts as a mitogen in prime surrounding cells for vaccinia infection []. Deletion of this growth factor causes decreased viral replication in resting cells and a 100-fold increase in the LD_{50} of intracranial vaccinia []. The combined effect of TK and VGF deletions on tumor specificity should be synergistic. In the

absence of TK, viral replication will require TTP from dividing cells. The normal stimulation of surrounding cells to divide will not occur in the absence of VGF; hence, replication will occur only in actively dividing cells." Thus, McCart *et al.* teaches that dramatically increased tumor specificity is, in fact, what one would expect to be the result of combined deletion of the TK and VGF genes based on the known properties of vaccinia virus and the role of the TK and VGF genes in viral infection. Therefore, contrary to Applicant's assertion, the cited art does not indicate that the properties of the vaccinia virus of the claims would be unexpected.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §103(a) as obvious over the art.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 12 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* as applied to claims 1 and 12 at pages 9-10 of the 12 May Office Action and herein above, and further in view of Paoletti (*supra*) as evidenced by UniProtKB/Swiss-Prot Database entry P04637, P53_HUMAN (hereinafter, P04637). Please note that P04637 is cited only to evidence properties that are inherent to the teachings of the art previously made of record and cited in the rejection of claims 1, 12 and 13 in the previous Office Action.

As stated in the 12 May Office Action at pages 9-10, the limitations of claims 1 and 12, as a whole, would have been obvious to one of ordinary skill in the art based on the teachings of Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.*

Claim 49 is directed to the composition of matter wherein the exogenous nucleotide sequence is a suicide gene. The specification, at paragraph 0035, teaches that suicide genes are genes that are involved in programmed cell death or apoptosis.

Paoletti, like Mastrangelo *et al.*, teaches cancer therapy using recombinant vaccinia virus vectors to elicit immune responses against tumor cells (see especially the abstract, the fourth full paragraph in column 6 and the paragraph bridging column 6-7). Paoletti further teaches that the inclusion of tumor associated antigens and administration directly into a tumor can elicit anti-tumor immune responses more rapidly and to sufficient levels to impede or halt tumor spread and potentially eliminate the tumor burden (third full paragraph in column 13 and the second full

paragraph in column 14). In that same paragraph, Paoletti goes on to identify p53 as among the tumor associated antigens known to be of immunotherapeutic value in the treatment of tumors.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* to include the tumor specific antigen p53 according to the teachings of Paoletti. Motivation to combine these teachings comes from the nature of the problem to be solved by the teachings of Mastrangelo *et al.*, which is to treat tumors by eliciting an immune response, and from the teachings of Paoletti, which indicate that inclusion of tumor associated antigens such as p53 can elicit anti-tumor immune responses more rapidly and to sufficient level to impede or halt tumor spread and potentially eliminate tumor burden (*Id.*). Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings in view of the teaching of Paoletti that p53 is among the tumor associated antigens known to be of immunotherapeutic value in treatment of tumors. Furthermore, as P04637 teaches that the p53 gene is involved in programmed cell death and apoptosis (see especially the section entitled "FUNCTION" on page 12 of 28) the p53 gene of Paoletti meets the limitations of the suicide gene of claim 49.

For these reasons, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as unpatentable over the art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER